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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,993	11/24/2003	Michele Cargill	CL1496ORD	3651

37492 7590 10/10/2008

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
10/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,993	CARGILL ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 7/15/08 has been entered.

2. Applicant is advised that should claim 45 be found allowable, claim 54 will be objected to under 37 CFR 1.75 as being a duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 44-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Each of these claims recites that the presence of particular nucleotides within a sequence context are "indicative of increased risk" or "indicative of decreased risk" but the claims are

silent as to what the risk is relative to. The use of the relative phrases "increased" and "decreased" without any basis for comparison is indefinite.

6. Claims 62-76 are further indefinite because the practice of the method could result in a determination that a single individual has both increased and decreased risk at the same time. The independent claim sets forth that the presence of a C (or G) is indicative of increased risk, while the presence of a T(or A) is indicative of decreased risk. A human individual, however, has two alleles and so could have both a C and a T, and it is confusing what the level of risk would be indicated by these claims.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 44-76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the

invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 44-52 and 54 are drawn to a method for identifying human who has an increased risk for developing Alzheimer's disease by determining the identity of a SNP in said human's nucleic acids "as represented by" position 101 of SEQ ID NO: 7368 or its complement wherein the presence of C at position 101 of SEQ ID NO: 7368 or G at position 101 of the complement of SEQ ID NO: 7368 is indicative of an increased risk for Alzheimer's disease.

Claims 53 and 55-61 are drawn to a method for identifying human who has an decreased risk for developing Alzheimer's disease by determining the identity of a SNP in said human's nucleic acids "as represented by" position 101 of SEQ ID NO: 7368 or its complement wherein the presence of T at position 101 of SEQ ID NO: 7368 or A at position 101 of the complement of SEQ ID NO: 7368 is indicative of an decreased risk for Alzheimer's disease. However, while the study in the specification found that the C allele is present more often in individuals having Alzheimer's disease than the T allele, the specification has not shown that the presence of a single T allele is sufficient to indicate a "decreased" risk relative to the general population nor relative to individuals who are homozygous for the "C" allele, an embodiment which the claims encompasses.

Claims 62 combines claims 44 and 52, setting forth that the method is for determining the human's risk for developing Alzheimer's disease. In the practice of this method an individual who is homozygous at this SNP position will be determined to have both increased and decreased risk for developing disease. The specification is silent as to the relative risk status of a homozygous individual.

Thus the nature of the claimed invention requires the knowledge of a reliable association between alleles of a single nucleotide polymorphism present at position 101 of SEQ ID NO: 7368 and altered risk for developing Alzheimer's disease.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

Wang teaches the polymorphism elected for prosecution, namely, nucleotides 395-595 of SEQ ID NO: 5 taught by Wang (US 2003/0204075) are identical to instant SEQ ID NO: 7368, including the indication of a C/T polymorphism at position 495 of the sequence taught by Wang (this position aligns with instant position 101 of SEQ ID NO: 7368). Wang does not teach any relationship between alleles of this polymorphism and Alzheimer's disease.

Further, the art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility. Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population

diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

Indeed, the unpredictability of the instantly claimed invention is specifically discussed in the post-filing date references of Bertram et al. (The American Journal of Human Genetics, Volume 79, pages 180-183), Minster et al. (Neuroscience Letters 408(206) 170-172), and Liang et al. (Annals of Human Genetics, 2008, Vol. 72, pages 141-144). In all three of these references, the relationship set forth in the instant claims, namely between a polymorphism at position 101 of SEQ ID NO: 7368 and an altered likelihood of developing Alzheimer's disease was unable to be replicated. Further, it is noteworthy any association suggested by the data in Bertram et al. suggest that the opposite allele is related to disease (Bertram et al., p. 180). In response to the Bertram et al. paper, Grupe et al. (authorship including two of the instant inventors) state that "Further replication in well-characterized sample sets is required to assess whether the association is genuine (p. 184, Grupe et al. The American Journal of Human Genetics, Vol. 79, pages 183-184)." Having considered their study, the studies of Grupe et al., and Bertram et al., Liang et al. conclude that the SNP is not associated with LOAD (p. 144 and throughout).

Thus, even given the data in the specification, due to the highly unpredictable nature of this technology area, it remains highly unpredictable whether or not a reliable association exists between the polymorphism at position 101 of SEQ ID NO: 7368 and risk for Alzheimer's disease.

Guidance in the Specification.

The specification provides no evidence that any polymorphisms within SEQ ID NO: 7368 is reliably associated with any risk for developing Alzheimer's disease.

The specification teaches a case-control genetic study to determine the association of a large set of SNP in the human genome with late onset Alzheimer's disease (Example beginning

on page 117). The data suggest a putative relationship between the hCV8227677 SNP and late onset Alzheimer's disease in humans (see Table 6, page 5 of 6), however, in view of the high level of unpredictability in this technology area, these data are not sufficient to support the notion that there is a reliable association between alleles of this SNP and risk for Alzheimer's disease in humans.

The claims do not set forth teach what the increased risk is or decreased risk is relative to. The claim set forth increased risk or decreased risk when particular alleles are present, but do not provide what the increase or decrease is in relation to. Increase and decrease in the abstract are relative terms.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied prior to being able to practice the claimed invention as broadly as written. This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art teaches the unpredictability of associating polymorphisms with disease, and in particular the hCV8227677 polymorphism with Alzheimer's disease, it is unpredictable any polymorphisms is associated with altered risk any Alzheimer's disease in any individual. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized difficulties of association. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these

unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

8. Claims 71-76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a rejection for new matter. The examiner could not find any basis in the specification for the newly added claim limitations which require "providing a report." The response did not identify basis for these limitations and the examiner's review of the specification was unable to identify basis for the limitations.

Response to Remarks

Applicant discusses that the increased or decreased risk is relative to the other allele, pointing to the data in the specification to support this position. However, it is noted in the rejection that the claims are not limited to such a comparison. Furthermore, if this is the case, the claims fail to address what risk is present if both alleles are present. This is an area of confusion, particularly in claim 62 and those claims that depend from claim 62.

Applicant states that the art acknowledged finding that associations of genetic variations with disease may be irreproducible does not apply to the instant application since the association was observed in multiple independent studies. However, this is not persuasive in view of the

additional post-filing attempts to replicate these results which failed. It appears, that at the time of filing and even many years later it remains highly unpredictable whether a robust relationship between alleles of this polymorphism and Alzheimer's disease exist.

Applicant argues that the Hirschhorn and Ioannidis references do not support the allegation that the instant invention is not reliable because the instant specification includes replication. While these references alone may not support the allegation in view of Applicant's provided data, the totality of the teachings of the prior and later published references do support the position that the relationship, at best, is highly unpredictable.

Applicant points out that the relationship was replicated in four studies by Grupe et al. The authorship of this paper includes the inventors of this application. The studies of three independent groups, Bertram et al., Minster et al., and Liang et al. all failed to replicate the findings of Grupe et al., with the most recent paper concluding that there is no relationship between the SNP and late onset Alzheimer's disease.

Applicant points out that Grupe et al. provide a response to the Bertram reference. Again, it is noted that this paper has common authorship with the inventors of the instant application. In this reference the author's opinion is provided as to why Bertram et al. failed to find a relationship. This opinion paper cannot be considered as a replacement for evidence on the record, since there are parties on the paper who are also inventors (see MPEP 716.02(g)). Furthermore, even if the paper were filed in declaration form, however, Bertram et al. provide a different set of possible reasons for the discrepancy. The fact that additional groups (Minster et al. and Laing et al.) attempted to replicate the relationship and also failed weighs heavily on the conclusion that replication of this relationship in additional populations and studies is highly

unpredictable. Furthermore, as noted in the rejection, even though Grupe et al. state that Bertram's failure to replicate does not necessarily indicate the original association was a false-positive result, they also state "Further replication in well-characterized sample sets is required to assess whether the association is genuine." Further attempts at replication by Minster et al. and Liang et al. failed.

The rejection is maintained and applied to the newly added and amended claims.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Tuesday, or Wednesday, from 10:00 AM until 5:00 PM, and Thursday from 12:30 PM until 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

October 10, 2008